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The Preparation and Pyrolysis of 2-methyl-4-alkyl(aryl)semicarbazides

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THE PREPARATION AND PYROLYSIS OF 2-METHYL-4-ALKYL(ARYL)SEMICARBAZIDES

BY

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PYROLYSIS OF 2-METHYL-4-ALKYL(ARYL)SEMICARBAZIDES

This thesis is approved as a creditable and independent investigation by a candidate for the degree, Master of Science, and is acceptable as meeting the thesis requirements for this degree, but without implying that the conclusions reached by the candidate are necessarily the conclusions of the major department.

_____ Date

Thesis Adviser

_____ _____

Head, Chemistry Department Date

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INTRODUCTION

The purpose of the research described in this thesis was twofold. Attempts were made to prepare several 4-alkyl(aryl)-2-methylsemicarbazides, many of which had not been prepared previously. The successful synthesis involved the addition of alkyl and aryl isocyanates to methylhydrazine under controlled conditions. Secondly, the products from the pyrolysis of the semicarbazides were characterized and found to be 4-alkyl(aryl)-1-methylurazoles. The mechanism of the thermal reaction was elucidated. It was hoped, based on structural similarities to known active agents, that biologically active materials would be obtained. Products are currently undergoing evaluation for biological activity.

Anomalous behavior was observed upon the pyrolysis of 4-*t*-butyl-2-methylsemicarbazide. 4-Methylamino-1-methylurazole was obtained instead of the expected 1,4-dialkylurazole. An intramolecular rearrangement with dimethyl-*p*-urazine as an unstable intermediate would explain the result.

HISTORICAL

Unsubstituted semicarbazides have been prepared both as salts and as free bases. As an example, the electrolytic reduction of nitrourea in the presence of sulfuric acid yields semicarbazide sulfate[1]. The free base is obtained from the reaction of

$$NH_2C(O)NHNO_2 + H_2SO_4 + 6H \text{ (electrolytic)} \longrightarrow NH_2C(O)NHNH_2\ H_2SO_4 + H_2O$$

hydrazine with potassium isocyanate[2].

$$N_2H_4 + KNCO + H_2O \longrightarrow NH_2NHC(O)NH_2 + KOH$$

Several monosubstituted semicarbazides are also found in the literature. Phenylurea reacts with hydrazine hydrate to give 4-phenylsemicarbazide[3], while alkylnitrosoureas can be reduced to

$$C_6H_5NHC(O)NH_2 + N_2H_4\ H_2O \longrightarrow C_6H_5NH\ C(O)NHNH_2$$

2-alkylsemicarbazides[4].

$$ONNRC(O)NH_2 \xrightarrow{H_2/Pt} H_2NNRC(O)NH_2$$

Some disubstituted semicarbazides have also been prepared. 2,4-Diethylsemicarbazide, for example, has been obtained by reduction[5]. Phenyl isocyanate has been reported to react with the

$$CH_3CH_2N(NO)C(O)NHCH_2CH_3 \xrightarrow{H_2/Pt} CH_3CH_2N(NH_2)C(O)NHCH_2CH_3$$

substituted nitrogen of methyl- and isopropylhydrazine to yield 2-alkyl-4-phenylsemicarbazides[6]. With phenylhydrazine and phenyl

$$C_6H_5N=C=O \quad + \quad RNHNH_2 \longrightarrow C_6H_5NHC(O)NRNH_2$$

isocyanate however, the addition takes place at the unsubstituted nitrogen[7].

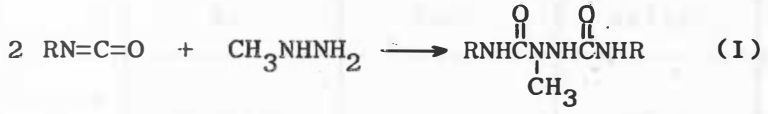
$$C_6H_5N=C=O \quad + \quad C_6H_5NHNH_2 \longrightarrow C_6H_5NHC(O)NHNHC_6H_5$$

The pyrolysis of disubstituted semicarbazides remains virtually unstudied. It has been shown that 1-phenyl-4-acylsemicarbazides rearrange to the 2-phenyl compounds upon heating[8].

$$RC(O)NHC(O)NHNHC_6H_5 \xrightarrow{\Delta} RC(O)NHC(O)N(C_6H_5)NH_2$$

DISCUSSION

The semicarbazides, Table I, were prepared by adding isocyanates to methylhydrazine. In concentrated solutions large quantities of 1,6-dialkyl(aryl)-3-methylbiureas, I, are produced due to double addition of the isocyanate to methylhydrazine. To eliminate double



$$2\ RN{=}C{=}O + CH_3NHNH_2 \longrightarrow RNHC(=O)N(CH_3)NHC(=O)NHR \qquad (I)$$

addition, the reactions were carried out in dilute benzene solution. Under this condition high yields of the desired monoaddition product were obtained.

The isocyanates may have reacted with methylhydrazine to give either II, III or both, although Michaelis[9], and later Smith[10], have reported that phenyl isocyanate adds only to the substituted nitrogen of methylhydrazine. The nmr spectra of the semicarbazides in all

$$RNHC(=O)N(CH_3)NH_2 \qquad (II) \qquad\qquad RNHC(=O)NHNHCH_3 \qquad (III)$$

cases contain only two absorptions for NH protons, integrating 2:1. Treatment of the semicarbazides with m-nitrobenzaldehyde yielded benzylidene derivatives, a reaction which is characteristic of a primary amino group. The nmr and chemical data therefore confirm addition at the substituted nitrogen.

Table I

Listed are physical data for compounds II, R given. The structure numbers refer to the number of the compound in this writing.

	R			
	cyclohexyl	n-butyl	phenyl	t-butyl
Structure Number	XVI	XVII	XVIII	XIX
Recrystallizing Solvent	$CH_3C{\equiv}N$	--	CCl_4	Cyclohexane
% Yield	66.5	58.0	60.0	69.0
mp (°C.)	141-143	--	88-90	100-102
bp (°C.)	--	107@0.4mm	--	--
mp of m-nitro-benzylidene derivative (°C.)	155-158	99-100	155-156	165-168

With the exception of 4-t-butyl-2-methylsemicarbazide, pyrolysis of the semicarbazides at 230 C. leads to the formation of 4-alkyl-(aryl)-1-methylurazoles, IV, Table II.

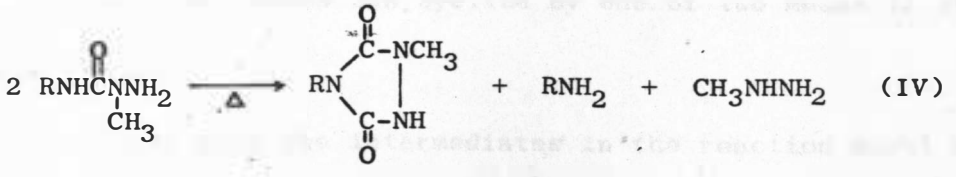


Table II

Listed are the physical properties of compounds IV, R given.

	R		
	cyclohexyl	phenyl	n-butyl
Structure Number	XXV	XXVII	XXVI
Recrystalizing Solvent	--	H_2O	--
% Yield	78.7	45.5	54.5
bp (°C)	155-165 @ 0.2 mm	250-260	195-200 @ 3.0 mm
mp (°C)	103-107	185-187	35-40

Mechanistically, there are two plausible routes for the formation of the substituted urazoles, Figure I. The transistion state for the first step is the same for both routes, and involves intermolecular condensation of two moles of the semicarbazide. Elimination of alkyl-(aryl)amine followed by cyclization of the 6-aminobiurea intermediate constitutes route A. In route B, methylhydrazine is eliminated to give a biurea intermediate, which can cyclize by one of two means to yield the urazole product.

It was thought that the intermediates in the reaction might be isolated if the reaction temperature was controlled. The melting

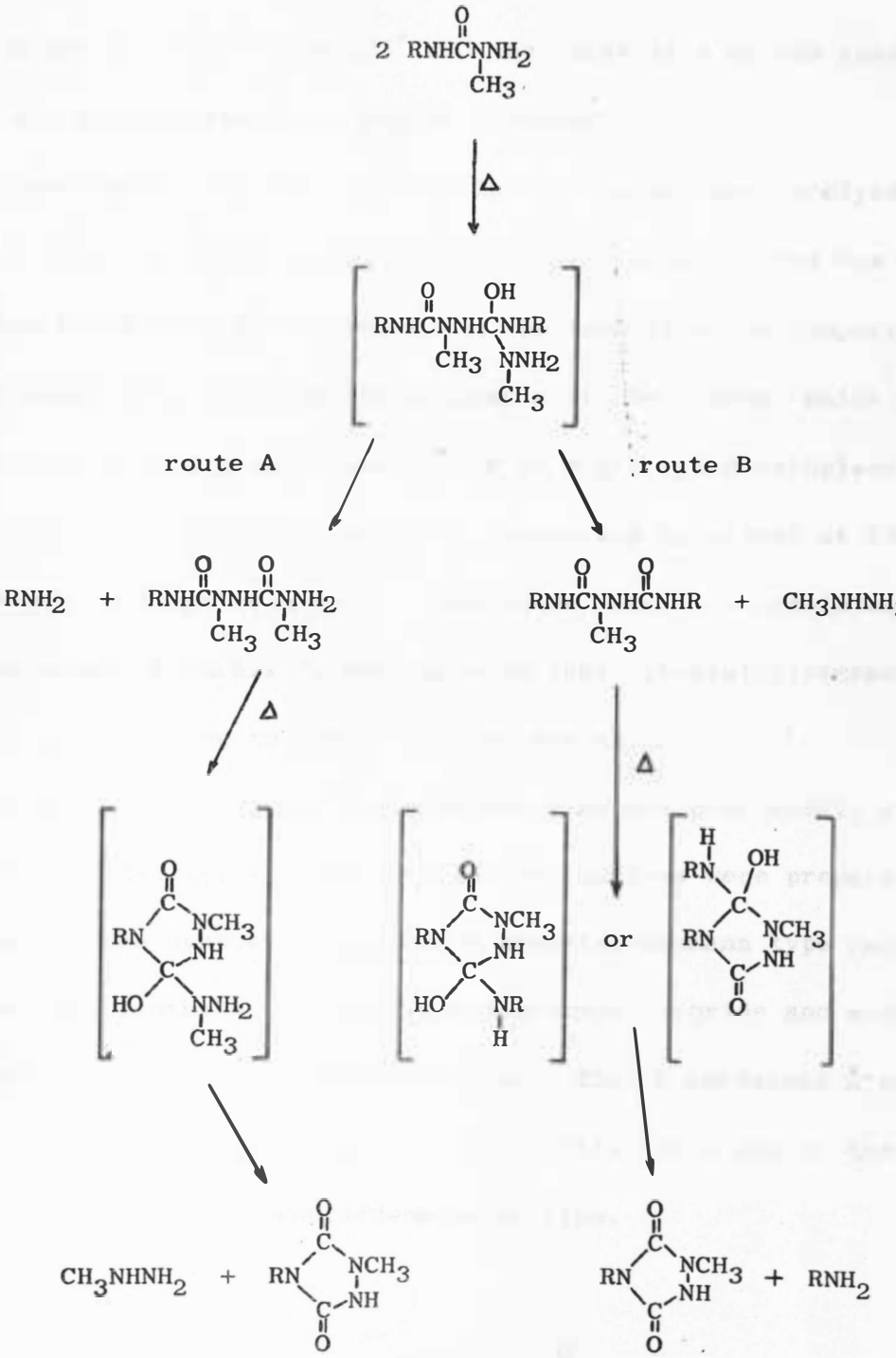


Figure I. Plausible mechanisms
for the pyrolysis of substituted semicarbazides.

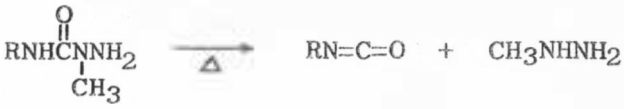
points of the biureas are in the range from 185-225°C. Thus, if the temperature was kept below 185° and the first step of the reaction occurred, the intermediates may be isolated.

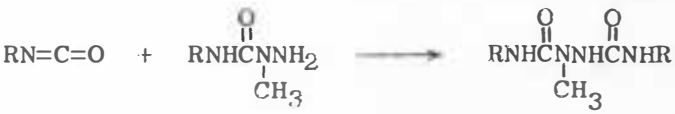
Accordingly, 4-n-butyl-2-methylsemicarbazide was pyrolysed for several hours at 150°C. and 1,6-di-n-butyl-3-methylbiurea was isolated from the reaction. The intermediate was identified by comparison of its physical data to an authentic sample of the biurea, which was prepared by adding n-butyl isodyanate to 4-n-butyl-2-methylsemicarbazide. The authentic sample of biurea was pyrolysed at 230°C. to give 4-n-butyl-1-methylurazole. The above result is consistent with that obtained by Furdik[11], who reported that 1,6-dialkylbiureas cyclize upon heating to give 4-alkyl-urazoles.

In an attempt to show that the reaction had gone solely via route B, 4,4-dialkyl(aryl)-2-methylsemicarbazides were prepared and pyrolysed. The synthesis involved a Schotten-Baumann type reaction between N,N-dimethyl- or N,N-diphenylcarbamyl chloride and methylhydrazine in alcoholic sodium hydroxide. That V contained a primary amino moeity was confirmed by its nmr spectral data and by the fact that it gave a m-nitrobenzylidene derivative.

$$R_2NC(O)Cl + CH_3NHNH_2 \xrightarrow[CH_3OH]{NaOH} R_2NC(=O)N(CH_3)NH_2 + NaCl \quad (V)$$

Lacking the necessary hydrogen atom, the 4,4-dialkyl(aryl)-2-methylsemicarbazides would be expected to condense and eliminate methylhydrazine to give the intermediate biurea but not cyclize. Pyrolysis of the 4,4-disubstituted compounds gave no methylhydrazine. No identifiable product could be recovered from the tarry residue. It is apparent that a free or at least incipient isocyanate is necessary for the preparation of the intermediate biurea. The 4,4-disubstituted semicarbazides could not yield a free or incipient isocyanate, being disubstituted at the 4-nitrogen. The first step of the proposed mechanism therefore must be modified.





To further elucidate the mechanics of the thermal reaction, a study was undertaken to determine the method of cyclization of the intermediate biurea. There are two routes by which the biurea might cyclize, Figure II.

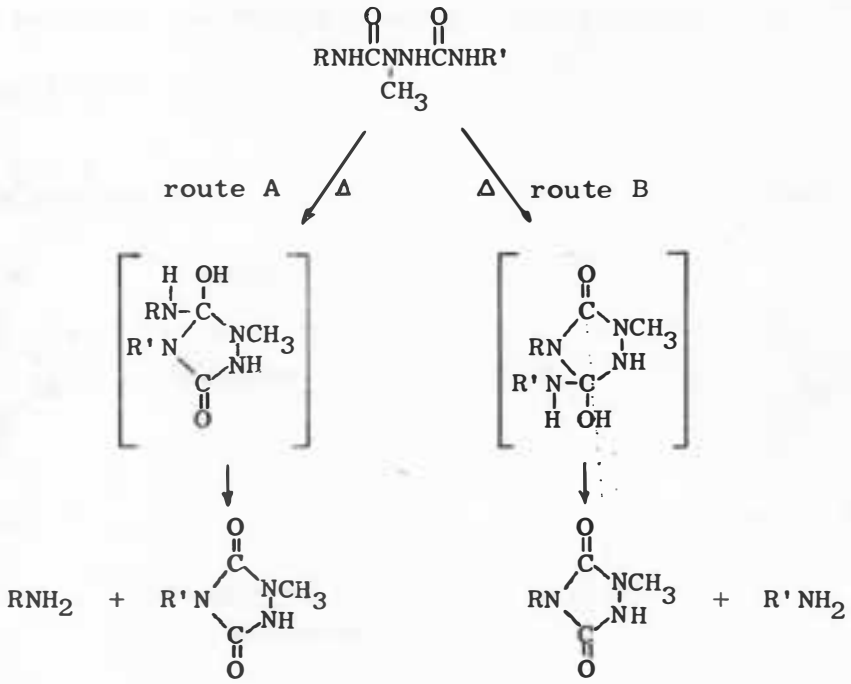


Figure II. Possible routes of biurea cyclization.

For the study, biureas VI and VII were synthesized by adding phenyl isocyanate to 2-methyl-4-n-butylsemicarbazide and n-butyl isocyanate to 2-methyl-4-phenylsemicarbazide. The possible

pyrolysis products via routes A and B for compounds VI and VII are outlined in Figure III.

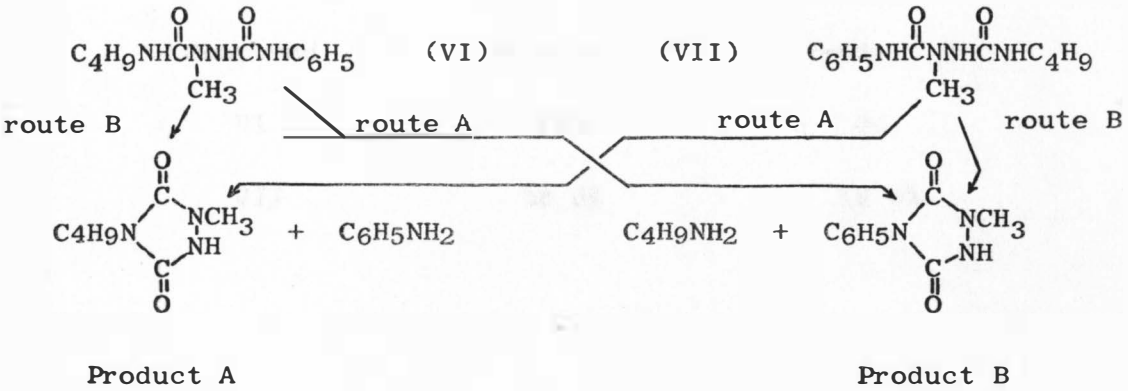


Figure III. Possible pyrolysis products of VI and VII.

The difference in the percentages of products A and B, Table III, can be rationalized on the basis of steric blocking of the adjacent carbonyl group by the methyl group. The lack of product B from VI is consistent with the lessened basicity of the 6-nitrogen compared to the 1-nitrogen due to the negative inductive and resonance effects of the phenyl group. The results show that the predominate route of cyclization of the intermediate biurea in the semicarbazide pyrolysis would be the least sterically crowded route, B.

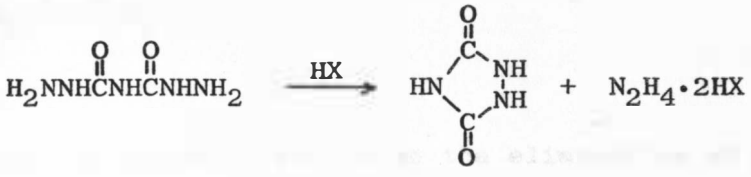
Urazole and some substituted analogs have been prepared previously. Both acidic and basic conditions have been utilized in their

Table III

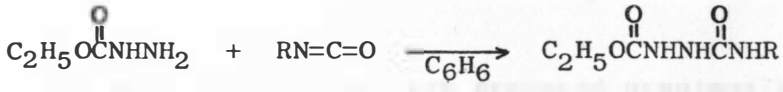
Listed are the percentages of products from mixed biurea pyrolysis.

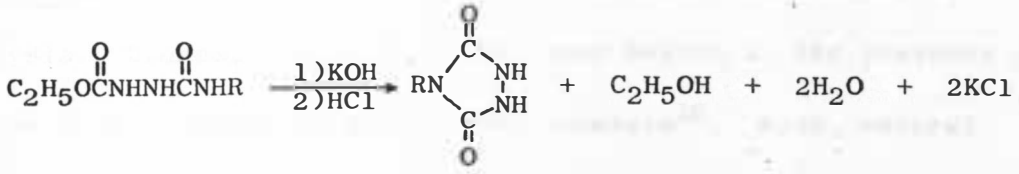
Compound	Product A	Product B
VI	80%	0%
VII	38.6%	13.6%

preparation. N,N'-diaminobiuret, for example, cyclizes in the presence of mineral acids to give urazole and hydrazine[12].

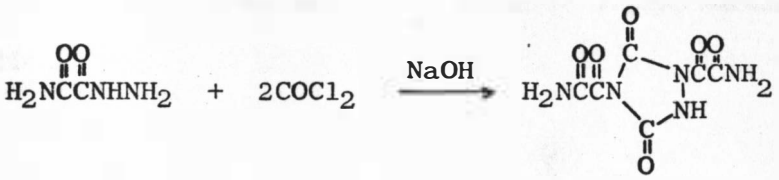


Zinner and Deuker[13] synthesized 4-phenyl- and 4-n-butylurazole by adding ethylcarbazate to phenyl and butyl isocyanate and allowing the product to cyclize in 4N potassium hydroxide. Similarly,

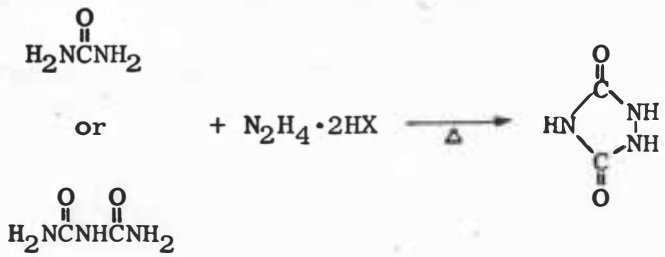




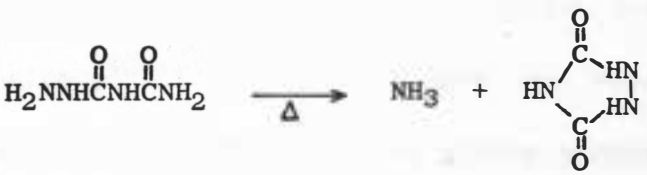
oxamic acid hydrazide has been cyclized to give 4-oxamida-1-oxamoylurazole[14].



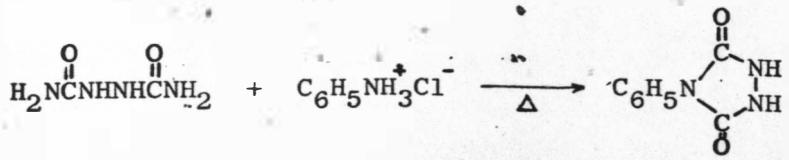
Pyrolysis reactions which yield unsubstituted urazoles are also known. The pyrolysis of urea or biuret in the presence of hydrazine salts results in the formation of urazole[15]. Also,



pyrolysis of aminobiuret results in the elimination of ammonia and the formation of urazole[16].

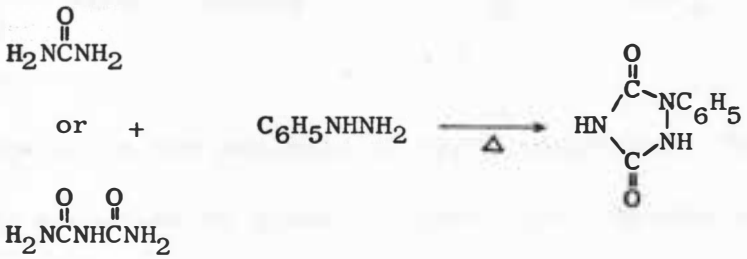


Monosubstituted urazoles have been prepared previously by pyrolysis. Biurea, for example, has been heated in the presence of aniline hydrochloride to give 4-phenylurazole[12]. Also, several

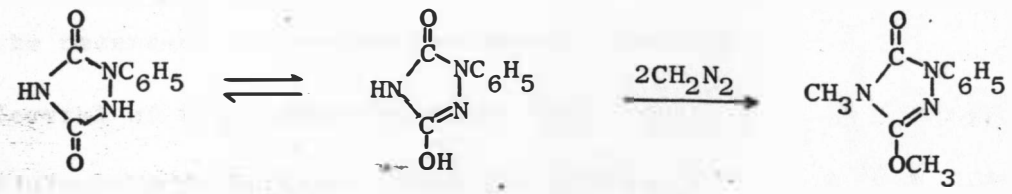


1,6-dialkylbiureas have been pyrolysed to give 4-alkylurazoles and alkylamines[11].

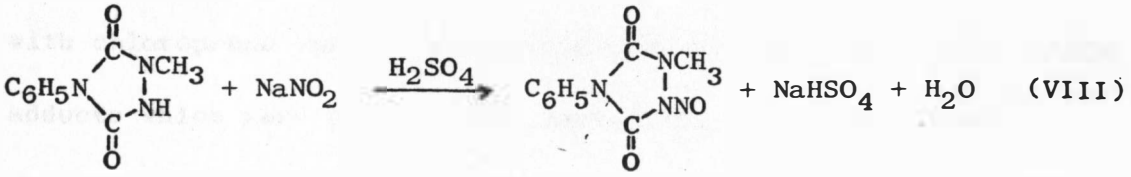
In addition, a single example of a 1-substituted urazole has been reported. The product was obtained by heating urea or biuret in the presence of phenylhydrazine[17].

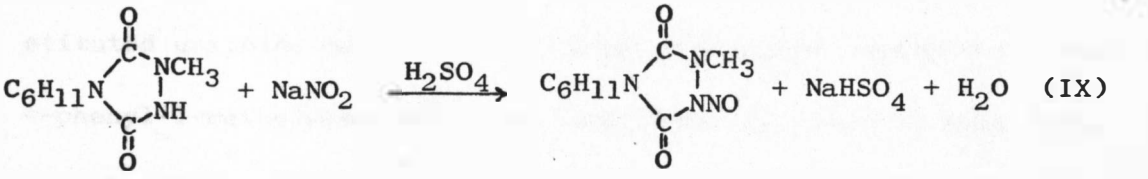


The chemistry of urazoles and 4-substituted urazoles has been studied extensively[11,12,18,19]. Some have been shown to exist to a small extent in the enolized form by giving minute yields of 3-methoxy derivatives upon reaction with diazomethane[20].



Among the reactions of urazoles that have not been investigated is nitrosation. In order to study this reaction, sodium nitrite was added to 1,4-disubstituted urazoles in 25% sulfuric acid solution. The reaction was carried out with 4-phenyl- and 4-cyclohexyl-1-methylurazole to give high yields of VIII and IX. Difficulties have



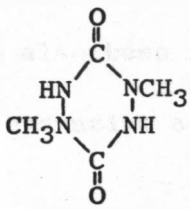


been encountered in the analysis of these compounds. To positively identify the structure of these new materials, further work is in order. Interestingly, the color of IX changes from white in the solid state to pale yellow in carbon tetrachloride or chloroform solution and pink in benzene or ethanol solution. The color changes indicate that IX may exist as a dimer in the solid state and become monomeric upon dissolution. Further studies with mass spectrometry would be necessary to confirm the dimeric structure.

Several of the disubstituted urazoles reported in this thesis may have biological properties. They are structurally similar to biologically active triazoles. For example, amizol, 3-amino-1,2,4-triazole

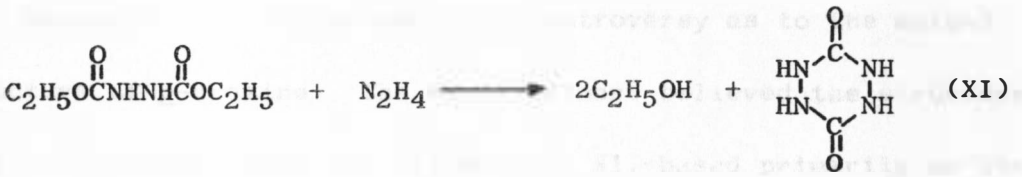
is effective as a herbicide[21]. The two isomers 1-methyl- and 2-methyl-3-(2-aminoethyl)-1,2,4-triazole possess histamine activity[22]. Also, certain triazoles may inhibit cholinesterase activity[23]. 4-Benzalurazole has been oxidized to 4-benzal-1,2,4-triazoline-3,5-dione with nitric acid. The resulting triazolinedione was treated with chloroprene and tetrachlorocyclopentadiene to give Diels-Alder adducts which were effective as herbicides and insecticides[11]. Urazole itself does not possess biological activity but no disubstituted urazoles have been evaluated previously, indeed only one, 4-phenyl-1-methylurazole[20], has been prepared prior to this work.

An anomalous pyrolytic reaction was observed with 4-t-butyl-2-methylsemicarbazide. Upon pyrolysis, t-butylamine was detected and a product formed whose elemental analysis corresponds to dimethyl-p-urazine, X, an unknown structure.



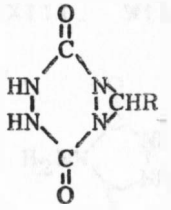
(X)

The first report of the preparation of p-urazine, XI, was by Curtius and Heidenreich[24,25], who prepared it by treating diethylbicarbamate with hydrazine. Their product was a monoacidic base forming silver, ammonium and barium salts. It reacted with aldehydes



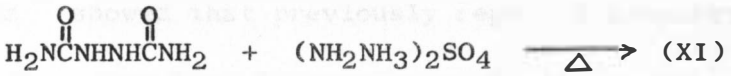
(XI)

in a 1:1 mole ratio to give a product which they incorrectly postulated to be XII. Purgotti[26] prepared p-urazine by heating biurea



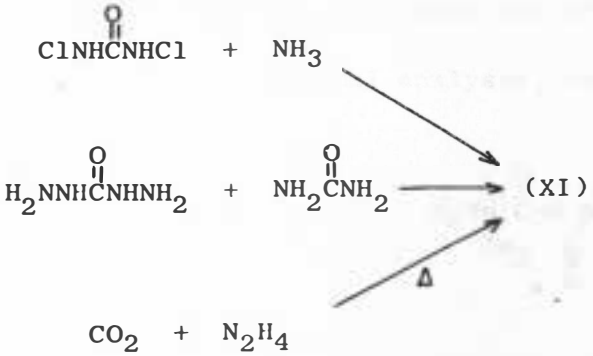
(XII)

with hydrazine sulfate and Purgotti and Vigano[27] reported that

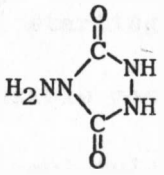


(XI)

p-urazine formed a dimethiodide. Other reports of the preparation of a p-urazine include that of Chattaway[28], who treated N,N'-dichlorourea with ammonia and Guhu and De[29], who treated carbohydrazide with urea. It has also been reported to be prepared by heating carbon dioxide with hydrazine at 100-300 atmospheres[30].



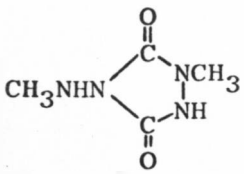
Recently, there has been much controversy as to the actual structure of p-urazine. The early authors believed the structure to be tetrahydro-3,6-s-tetrazinedione, XI, based primarily on the methods of synthesis. More recently, several authors have suggested that the structure is 1-amino-1,2,4-triazolidine-3,5-dione (4-aminourazole), XIII. Wiley[31], for instance, has reviewed



(XIII)

the old literature and concluded that the structure of p-urazine is XIII. Lutz[32] showed that previously reported preparations of p-urazine actually resulted in biureas or 4-aminourazoles. He confirmed the structures by high resolution mass spectroscopy, oxidation of the aminourazoles to urazole and structural characterization of the benzaldehyde derivatives. It is concluded that tetrahydro-3,6-s-tetrazinedione, XI has never been prepared.

In consequence, the product obtained from the pyrolysis of 4-t-butyl-2-methylsemicarbazide could have one of three structures, X, XIV or XV, based on its elemental analysis, the p-urazine



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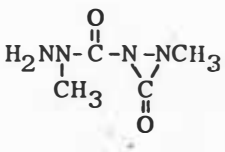
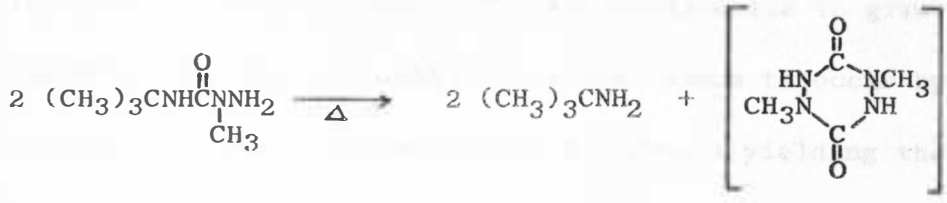
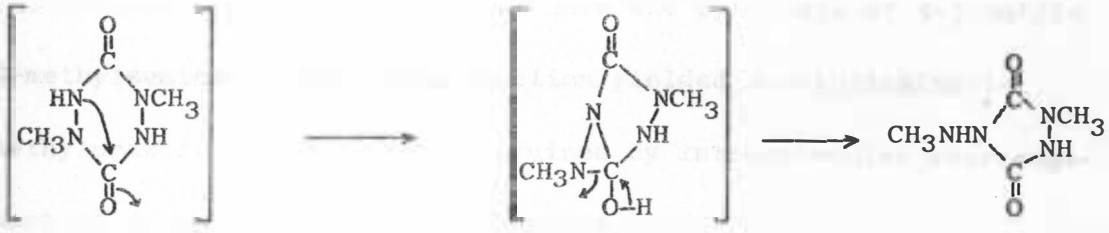


(XV)

structure being the less likely. Indeed, the nmr spectrum reveals two methyl absorptions, which eliminates X. An attempt to prepare a m-nitrobenzylidene derivative failed, thereby eliminating XV. The chemical and physical properties of the pyrolysis product are consistent with XIV.

The methyl group in XIV is two nitrogens from the carbonyl function, whereas, in the starting semicarbazide it is only one nitrogen removed. A plausible mechanism for the formation of XIV would involve an intramolecular rearrangement with dimethyl-p-urazine as an unstable intermediate.





SUMMARY

Several 4-alkyl(aryl)-2-methylsemicarbazides have been successfully prepared by reacting alkyl and aryl isocyanates with methylhydrazine in dilute benzene solution.

Pyrolysis of the disubstituted semicarbazides results in the formation of 4-alkyl(aryl)-1-methylurazoles, many of which have not been prepared previously. The mechanism of the thermal reaction involves dissociation to isocyanate and methylhydrazine followed by addition of the isocyanate to another mole of semicarbazide to give an intermediate 1,6-dialkyl(aryl)-3-methyl-biurea. The biurea cyclizes and eliminates a mole of alkyl(aryl)-amine to give the urazole product. The cyclization has been shown to occur by backside attack of the 1-nitrogen at the 5-carbonyl yielding the least sterically crowded transition state.

Anomalous behavior resulted upon the pyrolysis of 4-t-butyl-2-methylsemicarbazide. The reaction yielded 4-methylamino-1-methylurazole, which can be explained by intramolecular rearrangement of an unknown dimethyl-p-urazine.

N-Nitroso derivatives of 4-cyclohexyl and 4-phenyl-1-methylurazole were prepared, adding to the known chemistry of urazoles.

The new compounds reported in this thesis are currently being evaluated for biological activity.

LIST OF NEW COMPOUNDS

Disubstituted Semicarbazides

$\underline{n}\text{-}C_4H_9NHC(O)N(CH_3)NH_2$

$C_6H_{11}NHC(O)N(CH_3)NH_2$

$\underline{t}\text{-}C_4H_9NHC(O)N(CH_3)NH_2$

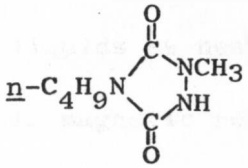
Trisubstituted Biureas

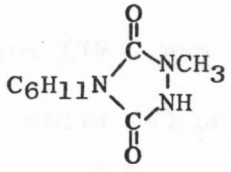
$\underline{n}\text{-}C_4H_9NHC(O)N(CH_3)NHC(O)NH(\underline{n}\text{-}C_4H_9)$

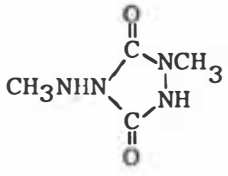
$C_6H_5NHC(O)N(CH_3)NHC(O)NH(\underline{n}\text{-}C_4H_9)$

$\underline{n}\text{-}C_4H_9NHC(O)N(CH_3)NHC(O)NHC_6H_5$

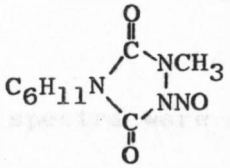
Disubstituted Urazoles

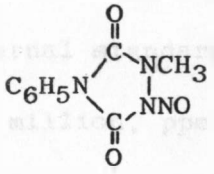






Nitrosourazoles





EXPERIMENTAL

The work reported herein was carried out in residence at South Dakota State University, Brookings, South Dakota.

Description of Instrumentation Used

Melting points of compounds XIX, XXVII and XXVIII were taken on a Thomas Hoover Capillary Melting Point Apparatus. All other melting points were determined in a Thiel Tube filled with parafin oil. All melting points are reported in degrees Centigrade and are uncorrected.

The infrared spectra were obtained on a Beckman IR-5 Spectrophotometer using NaCl plates. The solid samples were run as nujol mulls and the liquids as neat samples.

The nuclear magnetic resonance (nmr) spectra were obtained on a 60 MHz Varian A-60A Spectrometer. The solvent used is stated and tetramethylsilane (TMS) was used as an internal standard. The spectra are reported in delta (δ) units (parts per million, ppm).

Molecular weights were determined on a Mechrolab 301-A vapor pressure osmometer using a non aqueous probe. Freshly distilled ethanol was used as the solvent and the weights were determined graphically with benzil as a standard. The instrument was operated at 37.1°C.

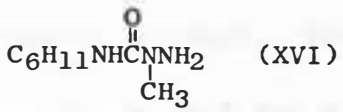
Liquid samples were chromatographed with a Beckman GC-2A Gas Chromatograph equipped with a Beckman general purpose column #74346. The stainless steel column measured 6' x $\frac{1}{4}$" and was packed with a ratio of 100 g of 42-60 mesh C-22 Johns-Manville firebrick to 30 g of Dow Corning silicone fluid, type 550.

Chemical analyses of compounds XXVI, XXVII and XXVIII were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Analyses of the other compounds were performed by Miss Agnes Leitheiser and Miss Sue Street at South Dakota State University, Chemistry Department, Brookings, South Dakota.

Preparation of 2-Methyl-4-cyclohexylsemicarbazide

Methylhydrazine, 13.8 g (0.3 mole), was dissolved in 450 ml of benzene and cyclohexyl isocyanate, 37.5 g (0.3 mole), was added dropwise with stirring. The mixture was stirred for one hour, cooled in an ice bath and suction filtered. The precipitate was recrystallized from acetonitrile. The yield of 2-methyl-4-cyclohexylsemicarbazide was 34.1 g (66.5%); mp 141-143 ; ir (nujol) 3300 cm^{-1} (NH), 3400 and 3200 cm^{-1} (NH_2), 1640 cm^{-1} (C=O), 1520 cm^{-1} (CONH), 750 cm^{-1} (NH); nmr ($CDCl_3$) 0.95-2.08 multiplet (10 H), 3.13 singlet (3 H), 3.50 broad (1 H), 3.78 singlet (2 H), 637 broad (1 H).

Structure:

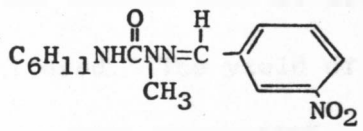


(XVI)

1-m-Nitrobenzylidene-2-methyl-4-cyclohexylsemicarbazide

2-Methyl-4-cyclohexylsemicarbazide, XVI, 0.171 g (0.001 mole), m-nitrobenzaldehyde, 0.3 g (0.001 mole) and three crystals of paratoluenesulfonic acid were placed in 15 ml of benzene and the solution refluxed for three hours. Benzene, 20 ml, was added and water removed by azeotropic distillation. The solvent was removed under reduced pressure to a volume of 10 ml. The precipitate was isolated by vacuum filtration, washed with ether and air dried. The yield of the benzylidene derivative was 0.31 g (100%); mp 155-158°; ir (nujol) 3350 cm^{-1} (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) 1.10-2.32 multiplet (10 H), 3.39 singlet (3 H), 3.50-4.00 broad (1 H), 6.45-6.83 broad (1 H), 7.53-817 multiplet (4 H).

Structure:



Preparation of 2-Methyl-4-n-butylsemicarbazide

Methylhydrazine, 13.8 g (0.3 mole), was dissolved in 450 ml of benzene and n-butyl isocyanate, 29.7 g (0.3 mole), was added

dropwise with stirring. The solution was stirred for one hour and the solvent removed under reduced pressure. Crude yield of the product was 40.73 g (91.6%). The product was distilled under vacuum and 2-methyl-4-n-butylsemicarbazide, 25.2 g (58%) was obtained; bp 107-109° (0.4 mm); ir (neat) 3300 cm^{-1} (NH), 3400 & 3200 cm^{-1} (NH_2), 1640 cm^{-1} (C=O), 1520 cm^{-1} (CONH), 760 cm^{-1} (NH); nmr ($CDCl_3$) 0.77 triplett (3 H), 1.00-1.45 multiplet (4 H), 2.89 singlet (3 H), 3.03 shoulder (2 H), 4.29 singlet (2 H), 6.50 triplet (1 H).

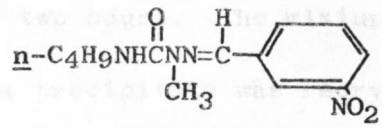
Structure:

(XVII)

1-m-Nitrobenzylidene-2-methyl-4-n-butylsemicarbazide

2-Methyl-4-n-butylsemicarbazide, XVII, 0.725 g (0.005 mole), m-nitrobenzaldehyde, 0.755 g (0.005 mole), and three crystals of paratoluenesulfonic acid were placed in 20 ml of ethanol and the solution refluxed for four hours. The solution was cooled in an ice bath and suction filtered. The yield of the benzylidene derivative was 1.08 g (78.2%); mp 99-100°; ir (nujol) 3310 cm^{-1} (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) 0.91 triplet (3 H), 1.17-190 multiplet (4 H), 3.29 triplet (2 H), 3.37 singlet (3 H), 6.70 triplet (1 H), 7.46-8.50 multiplet (5 H).

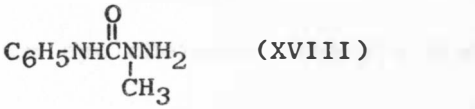
Structure:



Preparation of 2-Methyl-4-phenylsemicarbazide

Methylhydrazine, 9.2 g (0.2 mole), was dissolved in 300 ml of benzene and phenyl isocyanate, 23.8 g (0.2 mole), was added dropwise with cooling at 0-5°C. The mixture was stirred for one hour and allowed to come to room temperature. The precipitate was isolated by vacuum filtration and recrystallized from carbon tetrachloride. The yield of 2-methyl-4-phenylsemicarbazide was 19.68 g (60%); mp 88-90°; ir (nujol) 3300 & 3200 cm^{-1} (NH), 1660 cm^{-1} (C=O), 1520 cm^{-1} (CONH), 750 & 690 cm^{-1} (characteristic monosubstituted benzene absorption); nmr ($CDCl_3$) 3.01 singlet (3 H), 3.73 singlet (2 H), 6.45-8.26 multiplet (6 H).

Structure:



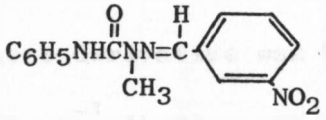
(XVIII)

1-m-Nitrobenzylidene-2-methyl-4-phenylsemicarbazide

2-Methyl-4-phenylsemicarbazide, XVIII, 0.825 g (0.005 mole), m-nitrobenzaldehyde, 0.755 g (0.005 mole), and three crystals of

paratoluenesulfonic acid were placed in 25 ml of ethanol and the solution refluxed for two hours. The mixture was cooled and suction filtered. The precipitate was recrystallized from ethanol and air dried. The yield of the benzylidene derivative was 1.16 g (78.5%); mp 155-156°; ir (nujol) 3400 cm^{-1} (NH), 1690 cm^{-1} (C=O), 1600 cm^{-1} (C=N), 1525 cm^{-1} (CONH), 690 & 750 cm^{-1} (typical mono-substituted benzene absorption); nmr ($CDCl_3$) 3.37 singlet (3 H), 6.95-8.21 multiplet (9 H).

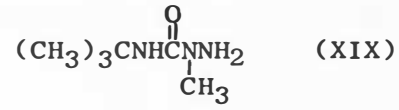
Structure:



Preparation of 2-Methyl-4-t-butylsemicarbazide

Methylhydrazine, 13.8 g (0.3 mole), was dissolved in 450 ml of benzene and t-butyl isocyanate, 29.7 g (0.3 mole), was added dropwise with stirring. The mixture was stirred for one hour and the solvent removed under reduced pressure. The solid residue was recrystallized from cyclohexane. The yield of 2-methyl-4-t-butylsemicarbazide was 30.3 g (69.0%); mp 100-102°; ir (nujol) 3400 and 3200 cm^{-1} (NH_2), 3300 cm^{-1} (NH), 1630 cm^{-1} (C=O), 1520 cm^{-1} (CONH), 760 cm^{-1} (NH): nmr (CCl_4) 1.23 singlet (9 H), 2.97 singlet (3 H), 3.85 broad (2 H), 6.28 broad (1 H).

Structure:

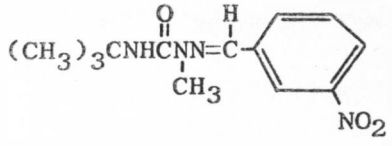


(XIX)

1-m-Nitrobenzylidene-2-methyl-4-t-butylsemicarbazide

2-Methyl-4-t-butylsemicarbazide, XIX, 2.9 g (0.02 mole), m-nitrobenzaldehyde, 3.0 g (0.025 mole), and ten crystals of para-toluenesulfonic acid were dissolved in 30 ml of ethanol and the solution refluxed for four hours. The yellow precipitate was isolated by vacuum filtration, washed with ether and air dried. The yield of the benzylidene derivative was 3.55 g (60%); mp 165-168°; ir (nujol) 1670 cm^{-1} (C=O), 1520 cm^{-1} (CONH), 1600 & 1500 cm^{-1} (aromatic C=C), 1380 cm^{-1} (gem-dimethyl absorption); nmr ($CDCl_3$) 1.36 singlet (9 H), 3.28 singlet (3 H), 6.53 singlet (1 H), 7.15-8.30 multiplet (5 H).

Structure:

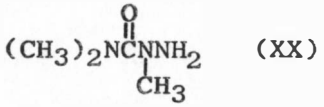


Preparation of 2,4,4-Trimethylsemicarbazide

To a solution of methylhydrazine, 18.4 g (0.4 mole), and sodium hydroxide, 16.0 g (0.4 mole), in 100 ml of methanol was added dropwise N,N-dimethylcarbamyl chloride, 43.0 g (0.4 mole),

with stirring and cooling. The sodium chloride was removed by filtration and the solvent removed under reduced pressure. The oily residue was distilled under vacuum and 2,4,4-trimethylsemicarbazide, 19.25 g (41.1%), was obtained; bp 56-58° (0.2 mm); ir (nujol) 3300 cm^{-1} (NH), 1625 cm^{-1} (C=O), 770 cm^{-1} (NH); nmr (CCl_4) 2.82 singlet (9 H), 4.02 singlet (2 H).

Structure:

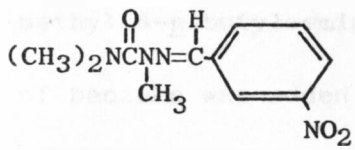


(XX)

1-m-Nitrobenzylidene-2,4,4-trimethylsemicarbazide

2,4,4-Trimethylsemicarbazide, XX, 1.0 g (0.0086 mole), m-nitrobenzaldehyde, 1.0 g (0.0066 mole), and three crystals of paratoluenesulfonic acid were dissolved in 30 ml of benzene and the solution refluxed for seven hours. The solvent was removed under reduced pressure and the solid residue recrystallized from ethanol. The yield of the benzylidene derivative was 1.16 g (70.8%); mp 128-131.5°; ir (nujol) 1640 cm^{-1} (C=O), 750 & 670 cm^{-1} (characteristic disubstituted benzene absorption); nmr ($CDCl_3$) 3.07 singlet (6 H), 3.29 singlet (3 H), 7.50-8.20 multiplet (5 H).

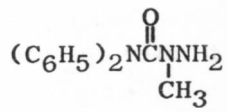
Structure:



Preparation of 2-Methyl-4,4-diphenylsemicarbazide

To a solution of methylhydrazine, 4.6 g (0.1 mole), and sodium hydroxide, 4.0 g (0.1 mole), in 100 ml of methanol was added dropwise N,N-diphenylcarbamyl chloride, 23.1 g (0.1 mole), with stirring and cooling. The solution was stirred overnight. The sodium chloride was removed by filtration and the solvent removed under reduced pressure. The residue was distilled under vacuum and 2-methyl-4,4-diphenylsemicarbazide was obtained; bp 215° (15 mm); ir (neat) 3300 & 3200 cm^{-1} (NH_2), 3050 cm^{-1} (aromatic CH), 2950 cm^{-1} (aliphatic CH), 1650 cm^{-1} (C=O), 1600 & 1500 cm^{-1} (aromatic C=C), 750 & 690 cm^{-1} (typical monosubstituted benzene absorption); nmr (CCl_4) 3.72 singlet (3 H), 3.95 singlet (2 H), 6.74-7.38 multiplet (10 H).

Structure:



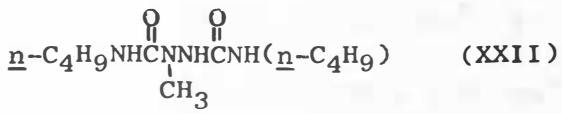
(XXI)

Analysis: Calculated for $C_{14}H_{15}N_3O$: C, 69.6; H, 6.22. Found: C, 73.4; H, 6.12.

Preparation of 1,6-Di-n-butyl-3-methylbiurea

To a solution of 2-methyl-4-n-butylsemicarbazide, XVII, 11.6 g (0.08 mole) in 100 ml of benzene was added n-butyl isocyanate, 7.92 g (0.08 mole), dropwise with stirring and very slight heating. The solution was warmed and stirred for one hour. The precipitate was isolated by vacuum filtration, washed with ether and air dried. The yield of 1,6-di-n-butyl-3-methylbiurea was 13.0 g (66.7%) mp 188-191°; ir (nujol) 3250 cm^{-1} broad (NH), 1640 cm^{-1} (C=O), 1520 cm^{-1} (CONH); nmr ($CDCl_3$, warmed) 0.91 triplet (6 H), 1.16-1.73 multiplet (8 H), 3.10 singlet (3 H), 3.15-3.40 multiplet (4 H), 6.17 broad (2 H), 7.24 singlet (1 H).

Structure:



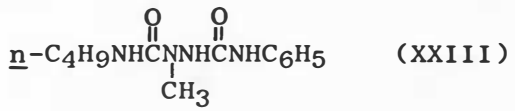
(XXII)

Preparation of 1-n-Butyl-3-methyl-6-phenylbiurea

To a solution of 2-methyl-4-n-butylsemicarbazide, XVII, 13.18 g (0.091 mole), in 250 ml of benzene was added phenyl isocyanate, 10.83 g (0.091 mole), dropwise with stirring. The mixture was stirred for two hours and suction filtered. The precipitate was washed with 50 ml of ether followed by 50 ml of chloroform and allowed to air dry in a hood overnight. The yield of 1-n-butyl-3-methyl-6-phenylbiurea was 22.8 g (95%); mp 187 - 190°;

ir (nujol) 3400-3200 cm^{-1} broad (NH), 1650 cm^{-1} (C=O), 1520 cm^{-1} (CONH).

Structure:

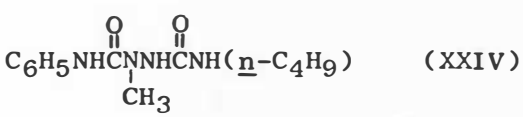


(XXIII)

Preparation of 1-Phenyl-3-methyl-6-n-butylbiurea

To a solution of 2-methyl-4-phenylsemicarbazide, XVIII, 16.5 g (0.1 mole), in 350 ml of hot carbon tetrachloride was added n-butyl isocyanate, 9.9 g (0.1 mole), dropwise with stirring. The solution was refluxed for three hours, filtered hot and cooled in an ice bath. The precipitate was isolated by vacuum filtration, washed with ether and air dried. The yield of 1-phenyl-3-methyl-6-n-butylbiurea was 16.4 g (62%); mp 190-192°; ir (nujol) 3300 & 3200 cm^{-1} (NH), 1665 cm^{-1} (C=O), 1600 & 1500 cm^{-1} (aromatic C=C), 1525 cm^{-1} (CONH).

Structure:



(XXIV)

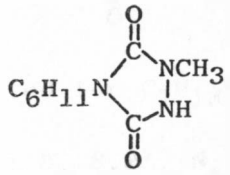
Pyrolysis of 2-Methyl-4-cyclohexylsemicarbazide

2-Methyl-4-cyclohexylsemicarbazide, XVI, 24.22 g (0.142 mole), was heated to 200-230°C. for two hours. A liquid distillate, 5.64 g, was collected and a thick yellow residue remained.

Gas chromatographic analysis of the liquid distillate showed the major portion to have the same retention time as an authentic sample of cyclohexylamine. A small portion of the sample had the same retention time as an authentic sample of methylhydrazine. The methylhydrazine portion of the sample was further characterized by spectral properties, preparation of a picrate derivative (mp 166-167°, Lit. 166°) and preparation of a sulfuric acid salt (mp 141-143°, Lit. 142°).

The yellow residue was distilled under vacuum, bp 155-165° (0.2 mm). The distillate was chilled in liquid nitrogen and the resulting hard solid material pulverized. The yield of 1-methyl-4-cyclohexylurazole was 11.0 g (78.7%); mp 103-107°; ir (nujol) 3100 cm^{-1} shoulder (NH), 1740 & 1650 cm^{-1} (C=O), 760 cm^{-1} (NH); nmr ($CDCl_3$) 1.10-2.65 multiplet (10 H), 3.21 singlet (3 H), 3.65-4.20 multiplet (1 H).

Structure:



(XXV)

Analysis: Calculated for $C_9H_{15}N_3O_2$: C, 54.8; H, 7.61. Found: C, 52.26; H, 7.09.

Molecular Weight Determination: Calculated for $C_9H_{15}N_3O_2$: 197. Found: 185.

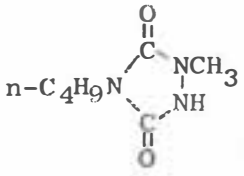
Pyrolysis of 2-Methyl-4-n-butylsemicarbazide

2-Methyl-4-n-butylsemicarbazide, XVII, 32.46 g (0.224 mole), was heated to 200-230°C. for three hours. A liquid distillate was collected and a colorless residue remained.

Gas chromatographic analysis of the liquid distillate showed the major portion to have the same retention time as an authentic sample of n-butylamine.

The residue was distilled under vacuum, bp 195-200° (3.0 mm), and crystallized after being chilled in liquid nitrogen. The yield of 1-methyl 4-n-butylurazole was 10.43 g (54.4%); mp 35-40°; ir (nujol) 3040 cm^{-1} shoulder (NH), 1750 & 1680 cm^{-1} (C=O), 760 cm^{-1} (NH); nmr (CCl_4) 0.90 triplet (3 H), 1.13-1.95 multiplet (4 H), 3.14 singlet (3 H), 3.45 triplet (2 H).

Structure:



(XXVI)

Analysis: Calculated for $C_7H_{13}N_3O_2$: C, 49.2; H, 7.60; N, 24.6. Found: C, 50.31; H, 8.21; N, 25.34.

Molecular Weight Determination: Calculated for $C_7H_{13}N_3O_2$: 171. Found: 162.

The pyrolysis of 2-methyl-4-n-butylsemicarbazide, XVII, was also carried out at 150° for fourteen hours. A liquid distillate was collected and a thick residue remained.

The liquid distillate was shown to be n-butylamine via its nmr spectrum; (CCl_4) 0.77 triplet (3 H), 1.0-1.45 multiplet (4 H), 2.51 multiplet (2 H), 3.60 singlet (2 H).

The residue was tritiated with ether until crystalline and recrystallized from acetonitrile. The yield of 1,6-di-n-butylbiurea was 1.2 g; mp 184-187°; ir (nujol) 3300 shoulder and 3200 cm^{-1} (NH), 1640 cm^{-1} (C=O), 760 cm^{-1} (NH); nmr ($CDCl_3$, warmed) 0.94 triplet (6 H), 1.15-1.80 multiplet (8 H), 3.12 singlet (3 H), 3.12-3.50 multiplet (4 H), 6.11 triplet (2 H), 7.20 singlet (1 H). The structure of the intermediate 1,6-di-n-butyl-3-methylbiurea was confirmed by comparison of ir and nmr spectra to the spectra of XXII.

Pyrolysis of 2-Methyl-4-phenylsemicarbazide

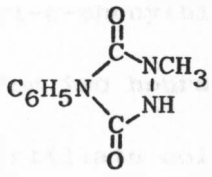
2-Methyl-4-phenylsemicarbazide, XVIII, 12.0 g (0.073 mole), was heated with an open flame. A liquid distillate was collected at 150-240° and a thick residue remained.

The liquid distillate was redistilled under vacuum, bp 70° (10 mm). The yield of aniline was 3.1 g (0.033 mole). The

structure was verified by comparison of its ir spectrum with the spectrum of an authentic sample of aniline.

The residue was distilled, bp 250-260°, and solidified in the collection flask. The solid was recrystallized from water and air dried. The yield of 1-methyl-4-phenylurazole was 3.15 g (45.5%); mp 185-187°; ir (nujol) 3200 cm^{-1} shoulder (NH), 1740 & 1665 cm^{-1} (C=O), 750 & 690 cm^{-1} (typical monosubstituted benzene absorption); nmr (DMSO-d^6) 2.99 singlet (3 H), 7.35 singlet (5 H).

Structure:



(XXVII)

Analysis: Calculated for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.98. Found: C, 56.49; H, 4.90; N, 21.80.

Molecular Weight Determination: Calculated for $C_9H_9N_3O_2$: 191. Found: 190.7.

Pyrolysis of 1,6-Di-n-butyl-3-methylbiurea

1,6-Di-n-butyl-3-methylbiurea, XXII, 8.95 g (0.0367 mole), was heated to 215-230° for one hour. A liquid distillate, 1.37 g, was collected and a colorless liquid residue remained.

The liquid distillate was shown to be n-butylamine by comparison of its nmr and ir spectra to the spectra of an authentic sample of n-butylamine.

The colorless residue was distilled under vacuum, bp 131-135° (0.20 mm), and 1-methyl-4-n-butylurazole, 6.10 g (97.2%), was obtained. The ir and nmr spectra compare exactly to the spectra of XXVI.

Pyrolysis of 1-n-Butyl-3-methyl-6-phenylbiurea

1-n-Butyl-3-methyl-6-phenylbiurea, XXII, 11.87 g (0.045 mole), was heated to 230°C. for two hours. A vacuum was drawn on the sample and a liquid distillate collected, leaving a colorless residue.

Gas chromatographic analysis of the liquid distillate indicated essentially pure aniline with identical retention time as an authentic sample.

The residue was dissolved in carbon tetrachloride and the solution suction filtered. The solvent was removed under reduced pressure and the residue distilled under vacuum. The yield of 1-methyl-4-n-butylurazole was 6.15 g (81.0%); bp 157-160° (0.75 mm). The nmr and ir spectra compare exactly to the spectra of XXVI.

Pyrolysis of 1-Phenyl-3-methyl-6-n-butylbiurea

1-Phenyl-3-methyl-6-n-butylbiurea, XXIV, 10.0 g (0.038 mole), was heated to 230°C. for three hours. A liquid distillate, 0.45 g, was collected and a clear residue remained. A vacuum was drawn on the residue and, with heating, another liquid distillate, 2.02 g, collected.

Gas chromatographic analysis of the lower boiling liquid distillate indicated two components. One component (60%) had the same retention time as an authentic sample of n-butylamine. The other component (40%) had the same retention time as an authentic sample of aniline. Analysis of the higher boiling liquid distillate indicated essentially pure aniline with identical retention time as an authentic sample.

Carbon tetrachloride was added to the residue. The insoluble material was isolated by vacuum filtration, recrystallized from water and found to be 1-methyl-4-phenylurazole, 2.1 g (29%); mp 183-187°. The ir and nmr spectra compare exactly to the spectra of XXVII. The solvent was removed from the filtrate under reduced pressure and the residue distilled under vacuum. 1-Methyl-4-n-butylurazole, 2.4 g (37.7%), was obtained; bp 132-134° (0.15 mm). The ir and nmr spectra compare exactly to the spectra of XXVI.

Pyrolysis of 2,4,4-Trimethylsemicarbazide

2,4,4-Trimethylsemicarbazide, 8.1 g (0.069 mole), was heated to 230°C. for three hours. A liquid distillate was collected, which boiled upon warming to room temperature. The liquid was probably dimethylamine, bp 7°C. No definite compound could be isolated from the tarry residue which remained.

Pyrolysis of 4,4-Diphenyl-2-methylsemicarbazide

4,4-Diphenyl-2-methylsemicarbazide, 5.5 g (0.0228 mole), was heated to 235°C. for three hours. No liquid distillate was obtained and no decomposition appeared to occur. Upon heating above 250°C., the sample turned dark brown and tarry, yet no distillate was collected and no definite compound could be isolated from the tarry residue.

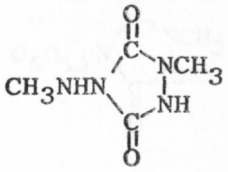
Pyrolysis of 2-Methyl-4-t-butylsemicarbazide

2-Methyl-4-t-butylsemicarbazide, XIX, 30.16 g (0.208 mole), was heated to 230°C. for one half hour. A liquid distillate, 13.0 g, was collected and a colorless residue remained.

Gas chromatographic analysis of the liquid distillate indicated essentially pure t-butylamine with the same retention time as an authentic sample.

The residue was tritiated with ether until crystalline and the solution suction filtered. The solid material was recrystallized from ethanol, allowing several hours for the crystals to appear. An attempt to prepare a m-nitrobenzylidene derivative of the product failed. The crude yield of 1-methyl-4-methylaminourazole was 10.0 g (66.6%); recrystallized, 4.5 g (30%); mp 149-150.5°; ir (nujol) 3280 cm^{-1} sharp (NH), 1750 & 1690 cm^{-1} (C=O), 1500 cm^{-1} (CONH), 750 cm^{-1} (NH); nmr (DMSO-d^6) 1.19 singlet (2 H), 2.47 singlet (3 H) 2.94 singlet (3 H); nmr (D_2O) 2.63 singlet (3 H), 3.16 singlet (3 H), 4.85 singlet (2 H, deuterium exchange).

Structure:



(XXVIII)

Analysis: Calculated for $C_4H_8N_4O_2$: C, 33.34; H, 5.56; N, 38.88. Found: C, 34.09; H, 5.82; N, 39.64.

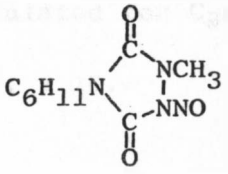
Molecular Weight Determination: Calculated for $C_4H_8N_4O_2$: 144. Found: 130.3.

Preparation of 1-Methyl-2-nitroso-4-cyclohexylurazole

To a warm solution of 25 ml of concentrated sulfuric acid in 100 ml of water was added 1-methyl-4-cyclohexylurazole, XXV, 1.97 g (0.01 mole). The solution was cooled to 0-5°C. in an ice bath

and a solution of sodium nitrite, 1.4 g (0.02 mole), in 40 ml of water added dropwise with stirring. The mixture was stirred for one half hour and suction filtered. The precipitate was washed with ether and air dried. The product was white, but gave yellow solutions when dissolved in carbon tetrachloride or chloroform and pink solutions in ethanol or benzene. The yield of 1-methyl-2-nitroso-4-cyclohexylurazole was 1.0 g (44.3%); mp 91-95°; ir (nujol) 1770 and 1650 cm^{-1} (C=O), the NH band of the starting urazole was lost; nmr (CCl_4) 1.10-2.35 multiplet (10 H), 3.12 singlet (3 H), 3.33-3.96 multiplet (1 H).

Structure:



(XXIX)

Analysis: Calculated for $C_9H_{14}N_4O_3$: C, 47.8; H, 6.19. Found: C, 52.59; H, 6.37.

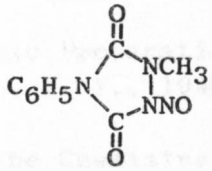
Molecular Weight Determination: Calculated for $C_9H_{14}N_4O_3$: 226. Found: 187.8.

Preparation of 1-Methyl-2-nitroso-4-phenylurazole

To a solution of 25 ml of concentrated sulfuric acid in 100 ml of water was added 1-methyl-4-phenylurazole, XXVII, 2.8 g (0.0147 mole). The solution was cooled to 0-5°C. in an ice bath

and a solution of sodium nitrite, 1.4 g (0.02 mole), in 40 ml of water added dropwise with stirring. The mixture was stirred for one half hour and suction filtered. The precipitate was washed with ether and air dried. The yield of 1-methyl-2-nitroso-4-phenylurazole was 2.03 g (62.8%); mp 109-111°; ir (nujol) 1770 & 1720 cm^{-1} (C=O), the NH band of the starting urazole was lost.

Structure:



(XXX)

Analysis: Calculated for $C_9H_8N_4O_3$: C, 49.1; H, 3.64. Found: C, 53.97; H, 4.10.

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